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NOTICE OF ALLOWANCE AND ISSUE FEE DUE

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WASHINGTON, DC 20004-1008

ISSUE FEE DUE 9-23-98

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
08/631,751	04/10/96	038	BARALYAR, H	1645 06/23/98
First Named Applicant:	SEATTLE, KENNETH L.			

TITLE OF INVENTION

MICROFABRICATED, FLOWTHROUGH POROUS APPARATUS FOR DISCRETE DETECTION OF BINDING REACTIONS

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 HARC0001	435-287.100	F71	UTILITY	NO	\$1320.00	09/23/98

**THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.**

**THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.**

**HOW TO RESPOND TO THIS NOTICE:**

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

- A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the Patent and Trademark Office of the change in status, or
- B. If the status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:

- A. Pay FEE DUE shown above, or
- B. File verified statement of Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

- I. Part B-Issue Fee Transmittal should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B Issue Fee Transmittal should be completed and returned. If you are charging the ISSUE FEE to your deposit account, section "4b" of Part B-Issue Fee Transmittal should be completed and an extra copy of the form should be submitted.

All communications regarding this application must give application number and batch number. Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

**IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.**

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1631751

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
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EXAMINER
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ART UNIT	PAPER NUMBER
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17

DATE MAILED:

### EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

- (1) Heather Bakalyn (3) \_\_\_\_\_  
(2) Paul Broth (4) \_\_\_\_\_

Date of Interview 6/17/98

Type: ☒ Telephonic ☐ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No. If yes, brief description: \_\_\_\_\_

Agreement ☒ was reached with respect to some or all of the claims in question. ☐ was not reached.

Claims discussed: Pending

Identification of prior art discussed: cited

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: \_\_\_\_\_

Authorization given for Exr Art.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

☒ 1. It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph below has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1-7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

☒ 2. Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the substance of the interview unless box 1 above is also checked.

Manual of Patent Examining Procedure, Section 713.04 Substance of Interview Must Be Made of Record

A complete written statement as to the substance of *any* face-to-face or telephone *interview* with regard to an application *must be made of record in the application*, whether or not an agreement with the examiner was reached at the interview.

§ 1.133 Interviews

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(b) In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be *filed* by the applicant. An interview does not remove the necessity for response to Office actions as specified in § 1.111, 1.135. (35 U.S.C. 132)

§ 1.2 Business to be transacted in writing. All business with the Patent and Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete a two-sheet carbon interleaf interview Summary Form for each interview held after January 1, 1978 where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks in neat handwritten form using a ball point pen. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below.

The interview Summary Form shall be given an appropriate paper number, placed in the right hand portion of the file, and listed on the "Contents" list on the file wrapper. The docket and serial register cards need not be updated to reflect interviews. In a personal interview, the duplicate copy of the Form is removed and given to the applicant (or attorney or agent) at the conclusion of the interview. In case of a telephonic interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the telephonic interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Serial Number of the application
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (personal or telephonic)
- Name of participant(s) (applicant, attorney or agent, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the claims discussed
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). (Agreements as to allowability are tentative and do not restrict further action by the examiner to the contrary.)
- The signature of the examiner who conducted the interview
- Names of other Patent and Trademark Office personnel present.

The Form also contains a statement reminding the applicant of his responsibility to record the substance of the interview.

It is desirable that the examiner orally remind the applicant of his obligation to record the substance of the interview in each case unless both applicant and examiner agree that the examiner will record same. Where the examiner agrees to record the substance of the interview, or when it is adequately recorded on the Form in an attachment to the form, the examiner should check a box at the Form informing the applicant that he need not supplement the Form by submitting a separate record of the interview.

It should be noted, however, that the interview Summary Form will not be considered and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview:

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

- 1) A brief description of the nature of any exhibit shown or any demonstration conducted.
- 2) an identification of the claims discussed.
- 3) an identification of specific prior art discussed.
- 4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the examiner.
- 5) a brief identification of the general thrust of the principal arguments presented to the examiner. The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application office. Of course, the applicant may desire to emphasize and fully describe those arguments which he feels were or might be persuasive to the examiner.
- 6) a general indication of any other pertinent matters discussed, and
- 7) if appropriate, the general results or outcome of the interview unless already described in the interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete or accurate, the examiner will give the applicant one month from the date of the notifying letter or the remainder of any period for response, whichever is longer, to complete the response and thereby avoid abandonment of the application (37 CFR 1.135(c)).

Examiner to Check for Accuracy

Applicant's summary of what took place at the interview should be carefully checked to determine the accuracy of any argument or statement attributed to the examiner during the interview. If there is an inaccuracy and it bears directly on the question of patentability, it should be pointed out in the next Office letter. If the claims are allowable for other reasons of record, the examiner should send a letter setting forth his or her version of the statement attributed to him. If the record is complete and accurate, the examiner should place the indication "interview record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Art Unit: 1645

### EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Paul Booth on 6/17/98.

2. The application has been amended as follows:

In claim 59, line 8, "in" is deleted and --on the walls of-- inserted.

In claim 59, line 10, "in" is deleted and --on the walls of-- inserted.

In claim 78, line 7, "in" is deleted and --on the walls of-- inserted.

In claim 78, line 9, "in" is deleted and --on the walls of-- inserted.

Claims 59-96 are renumbered 1-38, respectively.

3. Applicant is reminded that the PTO 948 indicates that the Figures are objected to by the Draftsman under 37 CFR 1.84 or 1.152. In order to avoid abandonment of the application, Applicant must make the specified changes and submit formal Drawings.

4. The following is an examiner's statement of reasons for allowance:

The recitations of "immobilized on the walls of ...channels" distinguish the instant invention from prior art microtiter vacuum manifolds (e.g. U.S. Patent 4,888,414, column 12,

Art Unit: 1645

lines 1-4) wherein binding reagents are bound to a nitrocellulose filter sandwiched between top and bottom portions of a 96-channel manifold substrate (reading on reagents immobilized inside channels). Immobilization of binding reagents on a two dimensional nitrocellulose binding surface which bissects a group of discrete channels does not fairly suggest the immobilization of the same reagents onto the actual surface of the channels' curved walls.

Though U.S. Patent 5,763,263 teaches an apparatus which can be used to screen for binding reactions comprising different test compounds immobilized on the inside walls of a set of tubes (e.g. claim 10), the set of tubes of U.S. Patent 5,763,263 does not fairly suggest the substrate having oppositely facing first and second major surfaces of the instant claims.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

5. Any inquiry concerning this communication should be directed to Heather Bakalyar at telephone number (703)305-7143.

The examiner can normally be reached on Monday through Friday from 9:00 am to 5:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, Ph.D., can be reached on (703) 308-4310. The official fax phone number for this Group is (703)308-4242.

6. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group 1800 receptionist whose telephone number is (703)308-0196.

Heather Bakalyar, Ph.D.  
6/18/98

Serial Number: 08/631,751

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Art Unit: 1645



**PAULA K. HUTZELL**  
**SUPERVISORY PATENT EXAMINER**

Art Unit: 1645

### DETAILED ACTION

1. The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1645.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The amendment filed 11/17/97 (Paper No. 12) is acknowledged and has been entered.

Claim(s) 1-11 and 13-16 has/have been canceled.

Claim(s) 21-58 has/have been added.

Claim(s) 12 and 17-58 is/are pending and subject to restriction/election requirement.

Claims 12 and 17-20 are withdrawn from consideration.

4. The amendment filed 11/17/97 (Paper No. 12) is objected to under 35 U.S.C. 132 because it introduces new matter into the specification. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the array element of claim 39, concepts of "discrete channels", "isolated channels" (not the same scope as "discrete regions or isolated regions" as per original claims) and the concept of a single well abutting a set or plurality of channels.

These new matter rejections may be obviated by Applicant pointing to explicit support in the specification or original claims by specific page and line number, or by Applicant pointing to implicit support accompanied by an explanation of how the cited text supports the alleged new matter.

Applicant is reminded that new matter is a written description issue.



***Claim Rejections - 35 U.S.C. § 112***

5. Claims 21-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. The recitation(s) of “set of channels” in claim(s) 21 and 23, lines 8-9 and 7-8, respectively, lack clear antecedent basis.

b. The recitation(s) of “adapted to receive” in claim(s) 36, 38-40 is/are vague and indefinite. It is unclear what structural modifications “adapted to receive” imparts to the claimed invention.

6. Claims 21-39, 41-58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The recitations of discrete or isolated channels, not the same scope as “discrete regions or isolated regions” as per original claims (e.g. claims 21 and 23), the concept of a single well abutting a plurality or “set” of channels (e.g. claim 36, 38, 39) and the array element of claim 39 do have descriptive support in the specification or claims as originally filed.

These new matter rejections may be obviated by Applicant pointing to explicit support in the specification or original claims by specific page and line number, or by Applicant pointing to implicit support accompanied by an explanation of how the cited text supports the alleged new matter.

Applicant is reminded that new matter is a written description issue.

7. Claims 36-38, 47-48, 57-58 are rejected under 35 U.S.C. 102(b) as being anticipated by Saiki et al PNAS (1989) 86 pages 6230-6234.

Saiki et al teach immobilization of oligonucleotide probes to a membrane substrate in spots (see Figures 2 and 3). In the absence of a definition for "channel" or "well" in the instant specification, the pores of the membrane read on wells on the membrane surface which are contiguous with channels that extend through the substrate such that the test sample (e.g. DNA, biomolecule) is capable of penetrating therethrough during the course of the hybridization (binding) reaction. Though the reference is silent in regard to the number of channels, one of skill in the art would expect the membrane to have  $10^7$  to at least  $3 \times 10^{10}$  channels per square cm, because the recited range is large and unlimited in the upper range, and the pores of the membrane are not visible to the naked eye.

8. Applicant's arguments filed 11/17/97 (Paper No. 12) have been fully considered but they are not persuasive. On page 8, Applicant argues that a nylon filter does not have discrete, aligned channels, and therefore permits lateral diffusion of materials. However, inspection of claims 36-38, 47-48, 57-58 reveals that the channels are not claimed to be discrete or isolated, or organized. Applicant is arguing limitations not in the claims.

9. Claims 21-58 are rejected under 35 U.S.C. 103(a) as being unpatentable Pirrung et al (U.S. Patent 5,143,854) in view of Tonucci et al (U.S. Patent 5,234,594) and Guirguis in further view of the known fact presented in the instant specification and Parham et al, BBRC vol 80 no 1 (1978) pages 1-6.

Pirrung et al teach synthesis of oligonucleotide arrays to make chemically diverse oligomers for screening for biological activity. This reference teaches that essentially any conceivable substrate may be used and that it may be desirable to physically separate synthesis regions for different polymers with wells, raised regions, etched trenches or the like (e.g. col 11,

lines 16-36; col 7, lines 49-57). Pirrung et al teach that the surface of the substrate is preferably provided with a layer of linker molecules, which are of a sufficient length to permit polymers in a completed substrate to interact freely with molecules exposed to the substrate (see paragraph bridging columns 11-12) and the linker molecules are attached to glass surfaces via siloxane bonds (col 12, lines 30-40). In addition, on col 20, lines 1-26 Pirrung et al teach how one would synthesize all sixteen dinucleotides from four bases (reads on a fully degenerate set of oligonucleotides) each unique to a defined position in the array, and teaches the use of a microscope and fluorescent label to detect the binding reaction (reads on a detecting means which determines and reports the extent of a binding reaction, and as a charge-coupled device counts photons, fluorescence microscopy reads on detection via a charge coupled device. In the alternative, such a device is an obvious variant as both the instant microscopy and charge-coupled devices detect photons, and charge-coupled devices were well known at the time of invention). One of skill in the art would expect the oligonucleotides to be substantially homogeneous within a single position in the array due to the disclosed method of preparation of the array.

Pirrung et al fail to specifically teach the use of substrates which have discrete and isolated regions that extend through the substrate, such as nanoporous glass.

Tonucci et al teach nanochannel filters (nanoporous wafer-like glass filters, see for example, Abstract) which have channels therethrough having an average diameter of less than one micron and in which the channels are present in high density (see col 3, lines 46-51 and Figure 5). Tonucci et al teach that the most unique properties of the nanochannel filter is the very small size of the channels which can reach  $10^{12}/\text{cm}^2$  (col 5, lines 51-66) (reads on a high or ultra-high density array of channels). This reference teaches that when a thin section of the nanochannel filter is acid etched completely through, it becomes an excellent filter, and that suction from below can be used

to pass a solution through the filter (reads on comprising a means for providing fluidic flow). In addition, this reference teaches that the nanochannel filter may be used in a variety of filtering conditions, and that the channels themselves may be straight or curved, (therefore one of skill in the art would expect channel shape was not critical), and may have a chemical lining on the walls (col 6, lines 24-30).

Guirguis teaches the advantages of using microporous membranes in immunoassays (which would apply to any specific binding assays, such as hybridization assays), in that filtration minimizes the diffusion limitation of the reaction rate due to the flow of reagents through the receptor-bearing membrane solid phase and the high ratio of microporous membrane surface to liquid volume (col 3, lines 12-29). In addition, this reference teaches that membrane substrates overcome many of the problems inherent in solid phase immunoassays as they combine the qualities of a solid substrate with a range of expanded capabilities and, due to their porosity and consequential large surface area, have a high binding capacity, which is measured by using smaller pore sized membranes whose total binding surface increases for an equivalent frontal surface (col 2, lines 15-23).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the nanoporous glass wafers taught by Tonucci et al as the substrate for the bimolecular arrays of Pirrung et al because this would allow for easy separation of free and bound target and because of the increased available surface area which allow for greater sensitivity, both well known advantages of filtration-based specific binding assays as well as for the teaching of Guirguis that membranes (which would include filters) have a high binding capacity, which is increased by using smaller pore sized membranes whose total binding surface increases for an equivalent frontal surface. Further, Tonucci teaches that when a thin section of

the nanochannel filter is acid etched completely through it becomes an excellent filter, and that suction from below can be used to pass a solution through the filter, and that the channels may have chemical lining on the walls (reads on oligonucleotide lining). In addition, it would have been obvious to use any desired shape of the wells and any desired density of the wells because Tonucci et al teach that the most unique properties of the nanochannel filter is the very small size of the channels and the high packing of the channels, which can reach  $10^{12}/\text{cm}^2$ , and that the shape of the channels is not critical. It is noted that Applicant has not pointed to the criticality of any of the recited dimensions of the regions (reads on channels) nor their packing density, therefore, such limitations are recognized results-effective variables and well within the purview of the skilled artisan in the absence of unexpected results. One of ordinary skill in the art at the time the invention was made would have been motivated to use the nanoporous glass wafers taught by Tonucci et al as the substrate for the bimolecular arrays of Pirrung et al because of the expectation of successfully making a high density, highly-sensitive device which would allow the simultaneous testing of multiple chemically diverse oligonucleotides for biological activity such as specific binding, or the ability to hybridize to test substances.

It may be determined that the siloxane bonds of Pirrung et al (U.S. Patent 5,143,854) in view of Tonucci et al (U.S. Patent 5,234,594) and Guirguis (5,244,815) which attach the polynucleotides to glass is differ from the bonds made by reaction of a terminal primary amine derivative of said polynucleotide to epoxysilane derivitized glass, and that triethylene glycol units are not incorporated.

However, page 23, line 25 through page 24, line 19 disclose that the chemistries involved in such reactions are well known for coupling amine-containing oligomers to glass.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the

time the invention was made to attach the polynucleotides to glass is differ by reaction of a terminal primary amine derivative of said polynucleotide to epoxysilane derivitized glass, and thereby incorporating triethylene glycol units because such chemistries are well known. One of ordinary skill in the art at the time the invention was made would have been motivated to attach the polynucleotides to glass is differ by reaction of a terminal primary amine derivative of said polynucleotide to epoxysilane derivitized glass, and thereby incorporating triethylene glycol units because of the expectation of successfully attaching polynucleotide to the device taught by the combination of Pirrung et al (U.S. Patent 5,143,854) in view of Tonucci et al (U.S. Patent 5,234,594) and Guirguis (5,244,815).

10. Claims 1-11, 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beattie et al, Clinical Chemistry 1993 and and Southern et al (Genomics 13 pages 1008-1017 (1992) (5,244,815) in view of Tonucci et al (U.S. Patent 5,234,594) and Guirguis (5,244,815).

Beattie et al teach genosensors comprising all oligonucleotide probes of a given length (e.g. 8-mer is 65,536 distinct probes, reads on fully degenerate) and teach DNA probe attachment to a glass surface through the use of siloxysilane and triethylene glycol phosphoryl spacers and teaches different methods such as the measurement of impedance of CCD arrays. Southern teaches a genosensor apparatus comprising multiple wells, each abutting and aligned with a plurality of channels. (See e.g. Figure 2). This organization provides the ability to load multiple channels with a particular nucleotide.

However, these reference differ from the instant invention in that it does not specifically teach the use of substrates which have discrete and isolated regions that extend throughout the substrate, such as nanoporous glass wafers.

Tonucci et al teach nanochannel filters (nanoporous wafer-like glass filters, see for example, Abstract) which have channels therethrough having an average diameter of less than one micron and in which the channels are present in high density (see col 3, lines 46-51 and Figure 5). Tonucci et al teach that the most unique properties of the nanochannel filter is the very small size of the channels which can reach  $10^{12}/\text{cm}^2$  (col 5, lines 51-66) (reads on a high or ultra-high density array of channels). This reference teaches that when a thin section of the nanochannel filter is acid etched completely through, it becomes an excellent filter, and that suction from below can be used to pass a solution through the filter (reads on comprising a means for providing fluidic flow). In addition, this reference teaches that the nanochannel filter may be used in a variety of filtering conditions, and that the channels themselves may be straight or curved, (therefore one of skill in the art would expect channel shape was not critical), and may have a chemical lining on the walls (col 6, lines 24-30).

Guirguis teaches the advantages of using microporous membranes in immunoassays (which would apply to any specific binding assays, such as hybridization assays), in that filtration minimizes the diffusion limitation of the reaction rate due to the flow of reagents through the receptor-bearing membrane solid phase and the high ratio of microporous membrane surface to liquid volume (col 3, lines 12-29). In addition, this reference teaches that membrane substrates overcome many of the problems inherent in solid phase immunoassays as they combine the qualities of a solid substrate with a range of expanded capabilities and, due to their porosity and consequential large surface area, have a high binding capacity, which is measured by using smaller pore sized membranes whose total binding surface increases for an equivalent frontal surface (col 2, lines 15-23).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the

time the invention was made to use the nanoporous glass wafers taught by Tonucci et al as the substrate for the genosensor of Beattie et al and Southern because this would allow for easy separation of free and bound target and because of the increased available surface area which allow for greater sensitivity, both well known advantages of filtration-based specific binding assays as well as for the teaching of Guirguis that membranes (which would include filters) have a high binding capacity, which is increased by using smaller pore sized membranes whose total binding surface increases for an equivalent frontal surface. Further, Tonucci teaches that when a thin section of the nanochannel filter is acid etched completely through it becomes an excellent filter, and that suction from below can be used to pass a solution through the filter, and that the channels may have chemical lining on the walls (reads on oligonucleotide lining). In addition, it would have been obvious to use any desired shape of the wells and any desired density of the wells because Tonucci et al teach that the most unique properties of the nanochannel filter is the very small size of the channels and the high packing of the channels, which can reach  $10^{12}/\text{cm}^2$ , and that the shape of the channels is not critical. It is noted that Applicant has not pointed to the criticality of any of the recited dimensions of the regions (reads on channels) nor their packing density, therefore, such limitations are recognized results-effective variables and well within the purview of the skilled artisan in the absence of unexpected results. One of ordinary skill in the art at the time the invention was made would have been motivated to use the nanoporous glass wafers taught by Tonucci et al as the substrate for the bimolecular arrays of Beattie et al because of the expectation of successfully making a high density, highly-sensitive genosensor device.

***Response to Arguments*** (103 rejections)

11. Applicant's arguments filed 11/17/97 (Paper No. 12) have been fully considered but they



are not persuasive.

Applicant argues the references of Pirrung et al, Tonucci et al and Guirguis, and Beattie et al, Tonucci et al and Guirguis cannot be combined because lithography will not work on a surface which is not flat. However, bridging paragraph, column 5-6 of U.S. Patent 5,585,968 teach that lithography on a curved surface, though more difficult than on flat, is supported by the state of the art.

Applicant also points to the different classifications of the patent references as evidence of non-analogous art. However, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). In this case, all references above encompass apparatus for analysis of biomolecules.

### ***Conclusion***

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire **THREE MONTHS** from the date of this action. In the event a first response is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than **SIX MONTHS** from the date of this final action.

13. Any inquiry concerning this communication should be directed to Heather Bakalyar at telephone number (703)305-7143.

The examiner can normally be reached on Monday through Friday from 9:00 am to 5:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, Ph.D., can be reached on (703) 308-4310. The fax phone number for this Group is (703)305-7939.

14. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group 1800 receptionist whose telephone number is (703)308-0196.

Heather Bakalyar, Ph.D.  
2/16/98

A handwritten signature in black ink, appearing to read 'A. Caputa', with a large, sweeping flourish at the end.

**ANTHONY C. CAPUTA  
PRIMARY EXAMINER  
GROUP 1800**